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MAJOR ARTICLE

Antiretroviral Drug Detection in a Community-Randomized Trial of Universal HIV Testing and Treatment: HPTN 071 (PopART)

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Background. Antiretroviral therapy (ART) reduces human immunodeficiency virus (HIV) transmission risk. The primary aim of this study was to evaluate ART uptake in a trial in Zambia and South Africa that implemented a community-wide universal testing and treatment package to reduce HIV incidence.

Methods. Study communities were randomized to 3 arms: A, combination-prevention intervention with universal ART; B, combination-prevention intervention with ART according to local guidelines; and C, standard of care. Samples were collected from people with HIV (PWH) during a survey visit conducted 2 years after study implementation: these samples were tested for 22 antiretroviral (ARV) drugs. Antiretroviral therapy uptake was defined as detection of ≥1 ARV drug. Resistance was evaluated in 612 randomly selected viremic participants. A 2-stage, cluster-based approach was used to assess the impact of the study intervention on ART uptake.

Results. Antiretroviral drugs were detected in 4419 of 6207 (71%) samples (Arm A, 73%; Arm B, 70%; Arm C, 60%); 4140 (94%) of samples with ARV drugs had viral loads <400 copies/mL. Drug resistance was observed in 237 of 612 (39%) viremic participants (95 of 102 [93%] with ARV drugs; 142 of 510 [28%] without drugs). Antiretroviral therapy uptake was associated with older age, female sex, enrollment year, seroconverter status, and self-reported ART (all $P < .001$). The adjusted risk ratio for ART uptake was similar for Arm A versus C (1.21; 95% confidence interval [CI], .94–1.54; $P = .12$) and Arm B versus C (1.14; 95% CI, .89–1.46; $P = .26$).

Conclusions. At the 2-year survey, 71% of PWH were on ART and 94% of those participants were virally suppressed. Universal testing and treatment was not significantly associated with increased ART uptake in this cohort.

Keywords. Africa; antiretroviral drugs; ART; HIV prevention; UTT.

Antiretroviral therapy (ART) reduces the risk of sexual human immunodeficiency virus (HIV) transmission [1, 2]. High ART coverage on a population level may reduce HIV incidence. However, population-level studies of universal HIV testing and treatment (UTT) have shown mixed results for reducing HIV incidence [3–7]. HPTN 071 (PopART) was a large, community-randomized trial that evaluated the impact of UTT on population-level HIV incidence in 21 communities in Zambia and South Africa (2013–2018) [6]. The study communities were matched into triplets based on geographic location, estimated HIV prevalence, and baseline ART coverage. In each triplet, communities were randomly assigned to 1 of 3 study arms. In Arm A, communities received a combination prevention intervention that included door-to-door HIV counseling and testing with universal ART (ART at any CD4 cell count). In Arm B, communities received the same combination prevention intervention with ART provided according to local guidelines, which shifted towards universal ART irrespective of CD4 count during the trial. In Arm C (control arm), communities received standard-of-care HIV testing services and ART according to local guidelines. The study included a Population Cohort of >48 000 adults in the study communities who had annual study visits. Samples from the Population Cohort were tested retrospectively at the HPTN Laboratory Center to

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determine HIV status and HIV viral load. The prevalence of viral suppression (viral load <400 copies/mL) among people with HIV (PWH) in the Population Cohort at the 2-year survey (2 years after study implementation) was 72% in Arm A, 68% in Arm B, and 60% in Arm C [6].

In this report, we measured ART uptake by assessing the portion of PWH in the HPTN 071 (PopART) Population Cohort who were taking antiretroviral (ARV) drugs at the 2-year survey. We also evaluated factors associated with detection of ARV drugs and the impact of the study intervention on ART uptake.

METHODS

Samples Used for Analysis

Plasma samples were obtained from participants enrolled in the Population Cohort of the HPTN 071 (PopART) trial (Clinical Trial Number: NCT01900977) at the 2-year survey [6, 8]. The Population Cohort included 48 302 participants (aged 18–44, 1 adult was randomly sampled from each randomly sampled household in the study communities). The study enrolled participants in annual surveys. Most participants were enrolled at the start of the trial (baseline survey); additional participants were enrolled in surveys conducted 1 and 2 years after the start of the trial. Participants were followed with annual study visits for up to 3 years and were tested for HIV at those visits. Participants who reported that they were HIV positive were asked whether they were previously on ART or were on ART at the time of the study visit. In both study countries, local guidelines for ART initiation changed during the trial [6]. At the start of the trial, the CD4 threshold for ART initiation was <350 cells/mm^3. The CD4 threshold for ART initiation increased to <500 cells/mm^3 in both countries in 2014. Universal ART was implemented in both countries in 2016. This report includes an analysis of samples from Population Cohort participants who tested positive for HIV infection at the 2-year survey (sample collection dates: August 2016 to July 2017).

Laboratory Assays

Plasma samples from the 2-year survey visit were tested for ARV drugs using a qualitative assay based on liquid chromatography coupled with high-resolution accurate mass spectrometry [9]. The assay detects 22 ARV drugs from 5 drug classes: 3 nonnucleoside reverse-transcriptase inhibitors (NNRTIs), 6 nucleotide/nucleoside reverse-transcriptase inhibitors (NRTIs), 9 protease inhibitors (PIs), 3 integrase strand transfer inhibitors (INSTIs), and 1 CCR5-antagonist (maraviroc). The limit of detection ranges from 5 ng/mL to 150 ng/mL, depending on the drug (Supplementary File 1).

Viral load testing was performed previously using the Abbott RealTime HIV-1 Viral Load assay (Abbott Molecular, Abbott Park, IL) (validated dilution method, limit of quantification: 400 copies/mL) [6]. Human immunodeficiency virus genotyping was performed previously to assess drug resistance in a randomly selected subset of samples from PWH with viral loads >400 copies/mL (21–30 participants per community) using the GenoSure MG assay (Monogram Biosciences, South San Francisco, CA) [10]. In this study, analysis of HIV drug resistance data was limited to participants who were HIV positive at study enrollment.

Statistical Analysis

Antiretroviral therapy uptake was defined as detection of at least 1 ARV drug. Viral suppression was defined as having a viral load <400 copies/mL. Factors associated with ART uptake were identified using logistic regression and adjusted for community.

In this community-randomized trial, assessments of intervention effect by study arm were based on community-level analysis. To assess viral suppression and ART uptake, we first determined the proportion of participants with each outcome in each community; the geometric means of these proportions were used to determine the proportion of participants with each outcome in each study arm. The impact of the HPTN 071 (PopART) intervention on ART uptake and viral suppression was assessed using a 2-stage analysis approach that is recommended for use in cluster-randomized trials with <15 clusters per group [11]. In the first step of the analysis, logistic regression was performed, adjusting for sex, age, interaction of age and sex, and triplet. This analysis was used to calculate the expected number of individuals on ART for each community under the null hypothesis of no intervention effect, adjusted for triplet, age, and sex composition. In the second step of the analysis, a two-way analysis of variance was performed on the adjusted log-ratio-residuals [log(observed number/expected number)] for each community, to estimate the intervention effect and corresponding P values; 95% confidence intervals (CIs) based on the residual sum of squares were computed on the log scale.

Patient Consent Statement

Written informed consent was obtained from all HPTN 071 (PopART) Population Cohort participants. Ethical approval for the trial was obtained from committees at the following institutions: the London School of Hygiene and Tropical Medicine, United Kingdom; the University of Zambia, Zambia; and Stellenbosch University, South Africa.

RESULTS

Detection of Antiretroviral Drugs

At the 2-year survey, 6259 participants in the HPTN 071 Population Cohort tested positive for HIV infection. Antiretroviral drug testing was performed for 6207 (99%) of

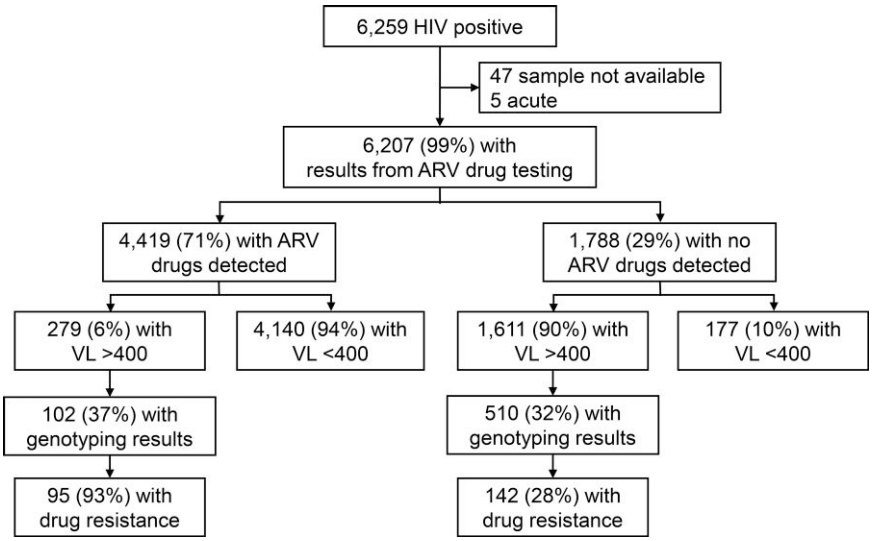

Figure 1. Study cohort. The figure shows the number of people with human immunodeficiency virus (HIV) at the 2-year survey visit and the number of those participants who had antiretroviral drugs detected, were virally suppressed, and had drug resistance. ARV, antiretroviral; VL, viral load.

those participants (1 sample/participant) (Figure 1). Of the 6207 participants with results from ARV drug testing, 82% were ≥25 years of age, 86% were women, and 97% had been living with HIV for >1 year. Antiretroviral therapy uptake was defined as detection of ≥1 ARV drug. At least 1 ARV drug was detected in samples from 4419 (71%) of the 6207 participants included in the assessment; 4140 (94%) of these participants were virally suppressed. In contrast, only 177 (10%) of the 1788 participants who had no ARV drugs detected were virally suppressed (Figure 1).

The 4419 samples with ARV drugs detected included 4217 (95%) samples with NNRTIs detected, 4194 (95%) samples with NRTIs detected, and 205 (5%) samples with PIs detected. None of the samples had INSTIs or maraviroc detected (Table 1). The most frequently detected NNRTIs were efavirenz ([EFV] 92%) and nevirapine (4%). The most frequently detected NRTIs were tenofovir (87%), lamivudine (64%), and emtricitabine (31%). The most frequently detected PIs were lopinavir (4%) and ritonavir (4%). The most common drug combinations detected were efavirenz/emtricitabine/tenofovir (75%) in South Africa and efavirenz/lamivudine/tenofovir (87%) in Zambia. Additional information is provided in Supplementary File 1.

Table 1. Antiretroviral Drugs Detected by Drug Class and Country[a]

ARV drugs	South Africa $n=2404$	Zambia $n=3803$	Total $n=6207$
≥1 ARV drug detected	1634 (68%)	2785 (73%)	4419 (71%)
NNRTIs	1498 (62%)	2719 (72%)	4217 (68%)
NRTIs	1503 (63%)	2691 (71%)	4194 (68%)
PIs	138 (6%)	67 (2%)	205 (3%)
INSTIs	0 (0%)	0 (0%)	0 (0%)
Maraviroc	0 (0%)	0 (0%)	0 (0%)

Abbreviations: ARV, antiretroviral drug; INSTI, integrase strand transfer inhibitor; NNRTI, nonnucleoside reverse-transcriptase inhibitor; NRTI, nucleotide/nucleoside reverse-transcriptase inhibitor; PI, protease inhibitor.

[a]The table shows the number and percentage of people with HIV who had 1 or more antiretroviral drug detected in each drug class at the 2-year survey.

Factors Associated With Antiretroviral Drug Detection

Among all PWH, detection of ARV drugs was significantly associated with age, sex, enrollment survey (baseline vs later), duration of HIV infection (<1 year or longer), and self-reported ART status (Table 2). Antiretroviral drugs were detected more frequently among participants ≥25 years compared to 18–24 years (76% vs 49%) and in women compared to men (73% vs 61%). Antiretroviral drugs were most frequently detected among women ≥25 years (77%), followed by men ≥25 years (64%), women 18–24 years (47%), and men 18–24 years (27%). Detection of ARV drugs was also higher in participants who enrolled in the study at baseline compared to those enrolled during the 2-year survey (71% vs 66%) and those who had HIV >1 year compared to those who acquired HIV infection in the prior year (73% vs 25%). Current ART was reported by 3546 (83%) of the 4262 participants who reported they were HIV positive; 3275 (92%) of those participants had ARV drugs detected. Antiretroviral drugs were also detected in 262 (37%) of 716 participants who reported that they were HIV positive but were not on ART.

As noted above, 4140 (94%) of the 4419 PWH with ARV drugs detected were virally suppressed. Participants aged ≥25 years old were more likely to be virally suppressed with ARV drugs compared to those 18–24 years old (94% vs 91%, $P=.04$). There was no difference in the proportion of men

Table 2. Factors Associated With Detection of ARV Drugs Among People With HIV in HPTN 071

Characteristic	Group	*n* (%) With ARV Test Results	*n* (%) With ARV Drugs Detected	OR (95% CI)	*P* Value
Age	18–24 years	1102 (18%)	536 (49%)	Reference	
	25 + years	5105 (82%)	3883 (76%)	3.79 (3.25–4.42)	<.001
Sex	Female	5343 (86%)	3893 (73%)	Reference	
	Male	864 (14%)	526 (61%)	0.40 (.23–.67)	<.001
Interaction of sex and age	Female, 18–24	720 (12%)	339 (47%)	Reference	.26
	Female, 25+	4623 (74%)	3554 (77%)	3.85 (3.27–4.53)	
	Male, 18–24	79 (1%)	21 (27%)	0.29 (.10–.82)	
	Male, 25+	785 (13%)	505 (64%)	1.37 (.80–2.41)	
Enrollment survey year[a]	Baseline	4533 (73%)	3240 (71%)	Reference	<.001
	1 year	724 (12%)	552 (76%)	1.18 (.98–1.43)	
	2 years	950 (15%)	627 (66%)	0.78 (.67–.91)	
Seroconverter[b]	No	5993 (97%)	4365 (73%)	Reference	.001
	Yes	214 (3.4%)	54 (25%)	0.12 (.09–.17)	
Current ART by self-report[c]	No	716 (17%)	262 (37%)	Reference	<.001
	Yes	3546 (83%)	3275 (92%)	20.3 (16.7–24.7)	

Abbreviations: ART, antiretroviral therapy; ARV, antiretroviral; HIV, human immunodeficiency virus; OR, odds ratio.

NOTES: The table shows the association of ARV drug detection with demographic and other factors. Data are shown for 6207 people with HIV in the HPTN 071 Population Cohort at the 2-year study visit. Results are adjusted for community.

[a]Most of the participants in the Population Cohort were enrolled at the start of the trial (baseline survey). Additional participants were enrolled during the 1-year survey or 2-year survey.

[b]Participants who tested negative for HIV infection at the 1-year survey and tested positive for HIV infection at the 2-year survey.

[c]Participants were only asked whether they were currently taking antiretroviral therapy if they reported that they had HIV.

versus women in the group of virally suppressed participants with ARV drugs detected (Supplementary File 2).

We also evaluated the proportion of persons who were virally suppressed but had no ARV drugs detected. Among the 4317 participants who were virally suppressed, participants aged 18–24 were more likely to be virally suppressed without ARV drugs compared to those ≥25 years old (11% vs 3%, $P < .001$). The proportion of participants who were virally suppressed without ARV drugs was also higher among those who acquired HIV infection in the prior year compared to those who had HIV for >1 year (21% vs 4%; $P < .001$). There was no difference in the proportion of men versus women in the group of virally suppressed participants with no ARVs detected (5% vs 4%, $P = .5$).

Human Immunodeficiency Virus Drug Resistance

Human immunodeficiency virus drug resistance was previously evaluated among a randomly selected subset of participants

Table 3. Impact of the HPTN 071 (Popart) Study Intervention on Uptake of Antiretroviral Therapy

Study Arm	No. of Participants With ARV Drugs Detected (%)[a]	Adjusted Risk Ratio (95% CI)[b]	*P* Value
ARV Drugs Detected Among PWH			
Arm A	1559/2148 (73%)	1.21 (.94–1.54)	.12
Arm B	1347/1883 (70%)	1.14 (.89–1.46)	.26
Arm C	1513/2176 (60%)	Reference	
Viral Suppression Among PWH			
Arm A	1524/2148 (71%)	1.16 (.98–1.37)	.07
Arm B	1314/1883 (67%)	1.09 (.92–1.29)	.27
Arm C	1479/2175 (60%)	Reference	
Viral Suppression Among PWH With ARV Drugs Detected			
Arm A	1466/1559 (94%)	1.01 (.99–1.04)	.16
Arm B	1257/1347 (93%)	1.00 (.98–1.03)	.65
Arm C	1417/1513 (93%)	Reference	

Abbreviations: ARV, antiretroviral; CI, confidence interval; PWH, people with human immunodeficiency virus.

NOTES: The table shows the proportion of people with human immunodeficiency virus (HIV) in different groups who had 1 or more ARV drug detected at the 2-year survey. Groups are based on results of ARV drug testing and HIV viral load testing (results from the 2-year survey). Data are shown for the each of the 3 study arms.

[a]The overall percentage of participants with 1 or more ARV drugs detected by arm is the geometric mean of percentages in the individual study communities. The percentage of participants with 1 or more ARV drugs detected for each community triplet is shown in Supplementary File 3. The overall percentage of participants with viral suppression by arm is the geometric mean of the rates of viral suppression in the individual communities.

[b]Adjusted for age, sex, age/sex interaction, and community.

who had a viral load >400 copies/mL 2 years after study implementation (see Methods). Human immunodeficiency virus genotyping results were available for 102 (37%) of 279 participants with ARV drugs detected and 510 (32%) of 1611 participants with no ARV drugs detected (Figure 1). Human immunodeficiency virus drug resistance was detected in samples from 95 (93%) of the 102 participants with ARV drugs detected and in samples from 142 (28%) of the 510 participants with no ARV drugs detected.

Impact of the Study Intervention on Antiretroviral Therapy Uptake

We next evaluated the impact of the HPTN 071 (PopART) intervention on uptake of ART by study arm (Table 3). The percentage of PWH who had ARV drugs detected at the 2-year survey was 73% in Arm A, 70% in Arm B, and 60% in Arm C. The adjusted risk ratio for ARV drug detection was 1.21 (95% CI, .94–1.54; $P = .12$) in Arm A versus C and 1.14 (95% CI, .89–1.46, $P = .26$) in Arm B versus C. The frequency of ARV drug detection in each community triplet is shown in Supplementary File 3.

The percentage of PWH who had ARV drugs detected in each of the 3 study arms (shown above) was similar to the percentage of PWH who were virally suppressed (71% in Arm A, 67% in Arm B, and 60% in Arm C) (Table 3). The percentage of virally suppressed participants among those with ARV drugs detected was high in all 3 study arms (94% in Arm A, 93% in Arm B, and 93% in Arm C). The adjusted risk ratio for viral suppression among those with ARV drugs detected was 1.01 (95% CI, .99–1.04, $P = .16$) in Arm A versus Arm C and 1.00 (95% CI, .98–1.03, $P = .65$) in Arm B versus Arm C.

Antiretroviral Therapy Coverage and Viral Suppression

As a final step, we evaluated the data in this report in the context of the UNAIDS goal of having 90% of persons with HIV aware of their status, having 90% of those persons on ART, and having 90% of those on ART virally suppressed [12]. In this report, over 70% of the PWH in the Population Cohort had ARV drugs detected after 2 years of study implementation (68% in South Africa; 73% in Zambia; 73% in Arm A). These results (for all participants, by country, and for Arm A alone) are below the goal of 81% for the first 2 UNAIDS targets (90% × 90%).

Viral suppression was observed for 94% of the participants with ARV drugs detected; this represents 66% of the PWH in the Population Cohort (70% × 94%). This is lower than the overall treatment target of 73% aware of their status, on ART, and suppressed (90% × 90% × 90%). In Arm A, 94% of the PWH who were on ART were virally suppressed with an overall result of 69% (73% × 94%). This is close to the 90-90-90 goal of 73% for all 3 of the UNAIDS targets. Results were similar for South Africa (68% on ART with 94% of those virally suppressed; overall result, 64%) and Zambia (73% on ART with 94% of those virally suppressed; overall result, 69%).

DISCUSSION

HPTN 071 (PopART) evaluated the impact of a combination prevention intervention on population-level viral load and HIV incidence. Increasing rates of viral suppression were observed in HPTN 071 (PopART) over time [6]. In the second survey year, the mean rate of viral suppression among persons with HIV in Arm A was 71.9% [6]. This is very close to the UNAIDS 90-90-90 target of 73% for all 3 goals. This is also close to the result obtained in this report for Arm A (69%), which was based on a direct biomedical assessment of ART coverage.

The ARV drug combinations detected in the samples were consistent with recommended ART regimens in Zambia and South Africa at the time of sampling (2016–2017, an NNRTI + 2 NRTIs). Few samples had PIs detected and none had INSTIs detected. Several factors were associated with detection of ARV drugs including female sex and older age. Similar results were observed in a 2017 national survey in South Africa [13]. In that report, ART coverage was 72% in women, 68% in men, 71% in those aged 25–49 years old, and 52% in those 15–24 years old. In this report, the lowest rate of ART was observed among younger men; additional efforts may be needed to reach this group. We also found that longer time on study and living with HIV for >1 year compared to <1 year were associated with detection of ARV drugs. Participants who were enrolled earlier and had HIV infection at earlier study visits would have had more opportunities for HIV testing and more time to access ART compared to those who enrolled at the 2-year survey or first tested positive for HIV infection at that visit. Self-report of ART was also associated with detection of ARV drugs. However, these data were not collected from all HIV-positive participants (those who did not report a prior positive HIV test were not asked about current ART). Among those who reported current ART, 8% did not have drugs detected. This may reflect poor ART adherence or inaccurate self-reported data. Furthermore, 37% of those who reported that they were HIV positive and not on ART had ARV drugs detected. Undisclosed ART has been observed in other research studies, clinic settings, and surveys [14–17]. This highlights the value of using a direct biomedical measure to assess ARV drug use.

We found that the frequency of HIV drug resistance was very high among those on ART who were not virally suppressed (93%). This could reflect a failure to achieve viral suppression in persons who were infected with drug-resistant HIV, acquisition of drug resistance due to suboptimal ART adherence, or other reasons. Viral suppression was also observed for 10% of those with no ARV drugs detected; further characterization of these cases revealed that ~40% of these participants were viremic controllers (data not shown).

Testing samples for ARV drugs can be costly in large studies and national surveys. Viral suppression is often used as a surrogate marker to assess ART uptake. In the HPTN 071 trial, viral suppression was a good surrogate for ART uptake; the prevalence of ART uptake measured by ARV drug testing was similar to the prevalence of viral suppression in the 3 study arms. Both measures indicated that although there was no statistically significant difference in ART uptake by study arm, there was a consistent trend for increased ART uptake in the intervention arms, especially for Arm A versus Arm C when measured by virally suppression only ($P = .07$) or by detection of ARV drugs ($P = .12$). Several factors may have promoted ART uptake in the Population Cohort over the course of the study, including the study interventions, increased ART availability with changes in local ART guidelines, or other factors.

This study has some limitations. First, the changes in local guidelines for ART initiation during the trial reduced the difference in access to ART in the UTT arm (Arm A) compared to the other 2 study arms that provided ART according to local guidelines. Second, the ARV assay used in this study only detects recent ARV drug dosing; ARV drugs may not have been detected in those with suboptimal adherence. In this study, 88% of the participants who had only 1 drug detected were using EFV; it is possible that some of those participants may have been using EFV for recreational purposes [18]. In this setting, NNRTIs and PIs are more likely to be detected than NRTIs due to their longer half-life; this may explain why some participants had an NNRTI or PI detected with no NRTIs detected. Third, the HPTN 071 Population Cohort included more women than men. Thus, the majority of samples tested for ARV drugs were from women (86%). Fourth, because of the large size of the trial, HIV drug resistance was only analyzed in a randomly selected subset of participants. Finally, in this study, we evaluated ART uptake in a single cross-sectional survey; we did not assess the use of ART over time or ART adherence.

CONCLUSIONS

In conclusion, after 2 years of study implementation, over two thirds of the PWH were taking ART and most of those people were virally suppressed. In this large community-randomized trial, viral suppression was an effective surrogate for evaluating ART uptake. This analysis also revealed a high rate of drug resistance among those on ART who were not suppressed. This highlights the importance of monitoring ART and addressing ART failure.

Supplementary Data

Supplementary materials are available at *Open Forum Infectious Diseases* online. Consisting of data provided by the authors to benefit the reader, the posted materials are not copyedited and are the sole responsibility of the authors, so questions or comments should be addressed to the corresponding author.

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Author contributions. All authors participated in the study, contributed to manuscript preparation, and reviewed the manuscript. J. M. F. designed the study, analyzed data, and drafted the manuscript; K. Z. performed statistical analyses and drafted the manuscript; W. A. C. provided scientific oversight for antiretroviral drug testing; E. P.-M. was the HPTN 071 QAQC Coordinator; A. B. performed antiretroviral drug testing; A. M. was the HPTN 071 Study Coordinator; B. K. and K. S. provided laboratory support for HPTN 071 in Zambia; G. v. Z. and M. S. provided laboratory support for HPTN 071 in South Africa; S. F. was the HPTN 071 Senior Statistician (LSHTM); P. B. was the HPTN 071 South African Site Co-Principal Investigator (PI); H. A. was the HPTN 071 Zambian Site PI; S. F. was the HPTN 071 Protocol Co-Chair; R. H. was the HPTN 071 Protocol Chair; D. D. was the HPTN 071 Protocol Statistician; S. H. E. was the HPTN 071 virologist, designed the study, analyzed data, and drafted the manuscript.

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Potential conflicts of interest. S. H. E. has performed collaborative research studies with Monogram Biosciences. All authors have submitted the ICMJE Form for Disclosure of Potential Conflicts of Interest. Conflicts that the editors consider relevant to the content of the manuscript have been disclosed.

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